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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,406	PETRONIS, ARTURAS	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21,23 and 24* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on March 27, 2007 is acknowledged. The response further elects the disease of bipolar disease and the restriction enzyme of AatII. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In the response, Applicants state that claims 11-19 and 21 have been amended so that they depend from claim 1 or claim 11. Applicants thereby conclude that these claims should be rejoined with the claims of Group I. However, claim 21 has been amended so that it refers back only to the non-Mendelian disease of claim 11. Claim 21 remains drawn to a method for isolating a probe. As set forth in the restriction requirement of February 27, 2007, this subject matter does not share a special technical feature of the subject matter of Group I of a method for detecting an epigenetic abnormality associated with a disease.

Accordingly, claim 21 is withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-19, 23 and 24 have been examined herein. Note that claims 9 and 12 have been examined only to the extent that the claims read on the elected invention of bipolar disorder and claim 18 has been examined only to the extent that the claim reads on the elected invention of the restriction enzyme AatII.

Information Disclosure Statement

2. The information disclosure statement filed March 30, 2006 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. In particular, the citation of "87 references . Please see attachment" has been lined through and has not been considered because this is not a proper citation to non-patent documents. The references recited on pages 2-8 of the IDS of March 30, 2006 have not been properly listed in the information disclosure statement because these pages do not include a separate column for initialing each reference or a signature field at the bottom of the listed references and these pages do not list the serial number of the application on each page of the list.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35

U.S.C. 119(e) as follows: A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a).

Since the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. However, Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, pages 9 and 33 of the specification). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, and10-19 are indefinite because the claims fail to recite a clear nexus between the preamble of the claims and the final step of the claims. The claims are drawn to a method for detecting an epigenetic abnormality. However, the claims recites only a single step of identifying a locus that is hypomethylated and an endogenous multi-copy DNA element. The claims do not set forth how detecting a hypomethylated locus and endogenous multi-copy DNA element results in the detection of an epigenetic abnormality associated with a disease. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for detecting a hypomethylated locus and endogenous multi-copy DNA element or methods for detecting an epigenetic abnormality associated with a disease. Further, in the latter case, it is unclear as to how the method results in the detection of an epigenetic abnormality associated with a disease.

Claims 1-9, 11-19 and 23 are indefinite and vague because it is not clear as to whether the method is one for detecting a locus having a hypomethylated sequence and detecting an endogenous multi-copy DNA element, or if the method is one for detecting a locus that comprises both a hypomethylated sequence and a multi-copy DNA element.

Claim 4 is indefinite over the recitation of "said disease-specific hypomethylated sequence" because this phrase lacks proper antecedent basis.

Claim 4 is indefinite over the recitation of "are within 10 kilobases of separation" because the claim does not set forth what the hypomethylated sequence and endogenous multi-copy DNA element are separated from.

Claim 5 is indefinite over the recitation of "normally methylated." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is unclear as to what is intended to be meant by normally methylated. For example, it is unclear as to whether this refers to methylation that occurs in one organism versus another organism, or methylation that occurs in one ethnic group versus another ethnic group, or methylation that occurs in individuals who do not have a disease or in individuals that are not susceptible to a disease.

Claim 7 is indefinite because the claim does not recite a clear nexus between the preamble of the claim and the final step of the claim and the claim omits essential process steps required to achieve the identification of a chromosomal region associated with a disease. The claims are drawn to a method for identifying a chromosomal region associated with a disease state. However, the claim recites only a single step of identifying a locus that is hypomethylated and an endogenous multi-copy DNA element. The claim does not set forth how detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element results in the identification of a chromosomal region associated with a disease. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element or methods for detecting a chromosomal region associated with a disease state. Further, in the latter

case, the claims do not recite the essential steps required to identify a chromosomal region associated with a disease state.

Claim 7 is indefinite over the recitations of "said diseased sample" and "the chromosomal region" because these phrases lack proper antecedent basis.

Claims 8 -9 and 19 are indefinite over the recitation of "proximal" because this phrase is not clearly defined in the specification to the extent that it refers to a locus and chromosomal sequence and there is no art recognized definition for what distance would be encompassed by a region proximal to a DNA coding sequence and a locus. It is also unclear as to what is intended to be meant by "1 to 10 coding sequences." It is unclear as to whether a single codon coding for an amino acid constitutes 1 of the 1 to 10 coding sequences or if this phrase is intended to refer to full length complete genes. Thereby, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claim 7 is also unclear over the recitation of "1 to 10 coding sequences." It is unclear as to whether a single codon coding for an amino acid constitutes 1 of the 1 to 10 coding sequences or if this phrase is intended to refer to full length complete genes. Thereby, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 8 and 9 are indefinite over the recitation of "said DNA sequence" because this phrase lacks proper antecedent basis. While the claims previously refer to a DNA and to a DNA coding sequence, the claim does not previously refer to a DNA coding

sequence. Further, it is unclear as to what is intended to be the relationship between the DNA coding sequence and the DNA sequence.

Claims 11-19 are indefinite because it is unclear as to the relationship between the steps recited in claims 11-19 and the step recited in claim 1, from which claims 11-19 depend. Claim 1 requires the step of identifying a locus that is hypomethylated. Claims 11-19 further comprise the steps of assigning a locus. It is unclear as to whether the steps of claims 11-19 are performed after the step of claim 1 (i.e., after the locus is detected, a locus is assigned). It is further unclear as to whether the locus of claim 1 is distinct or the same as the locus of claims 11-19 and it is unclear as to whether the sample analyzed in claims 11-19 is the same or distinct from the source of the eukaryotic sequences (locus and DNA element) identified in claim 1.

Claims 11-19 are indefinite over the recitation of "said sequence" in "g)" because it is not clear as to whether the sequence refers back to the sequence of the PCR product of step "f)" or the hypomethylated sequence.

Claim 19 is indefinite over the recitation of "said epigenetic abnormality comprises a gene" because it is unclear as to what is meant by an abnormality comprising a gene. Further, it is unclear as to how claim 19 is further limiting from claim 1 since claim 1 requires the detection of a genetic abnormality associated with a disease by detecting a locus in a eukaryotic genome, whereas claim 19 encompasses the detection of a disease in any organism (i.e., a eukaryotic or prokaryotic organism). Claim 19 is also indefinite and unclear over step i) since the claim does not clearly set forth the relationship between the test sample, the control sample and the sample of

claim 11 that was analyzed that exhibits characteristics of a non-Mendelian disease. It is unclear as to how the additional process steps recited in claim 19 of determining an expression pattern results in the detection of an epigenetic abnormality associated with a disease.

Claim 19 is indefinite over the recitation "corresponding" because "corresponding" is not an art recognized term to describe the relationship between two genes. It is not clear as to whether a corresponding gene refers to the identical gene or a gene sharing some unspecified level of identity with a first gene, or a gene that is a homologue or pseudogene of a first gene. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to nucleic acid sequences, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 23 and 24 are indefinite because the claims fail to recite a clear nexus between the preamble of the claims and the final step of the claims. The claims are drawn to a method for detecting disease associated with an epigenetic abnormality. However, the claims recite only a single step of identifying a locus that is hypomethylated and an endogenous multi-copy DNA element. The claims do not set forth how detecting a hypomethylated locus and endogenous multi-copy DNA element results in the detection of disease associated with an epigenetic abnormality. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for detecting a hypomethylated locus and endogenous multi-copy DNA element or

methods for detecting a disease associated with an epigenetic abnormality. Further, in the latter case, it is unclear as to how the method results in the detection of a disease.

Claim Rejections - 35 USC § 112 - Enablement

6. Claims 1-19, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-6 and 10-19 are drawn to methods for detecting an epigenetic abnormality associated with a disease comprising detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element. Claim 19 further includes the step of comparing expression patterns of a gene located proximal to said locus.

Claim 7 is drawn to a method for identifying a chromosomal region associated with a disease state comprising detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element.

Claims 8 and 9 are drawn to methods for identifying a DNA coding sequence having an epigenetically altered expression pattern comprising identifying a locus having a hypomethylated sequence and an endogenous multi-copy DNA element and comparing the expression patterns of DNA coding sequences.

Claims 23 and 24 are drawn to methods for diagnosing a disease associated with an epigenetic abnormality comprising detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element.

The claims as broadly written encompass the detection of any hypomethylated sequence wherein the sequence is not defined in terms of any particular chemical structure – e.g., a nucleotide sequence, it's location within a genome, the source of the sequence etc. Claims 1-5, 7-16, 18, 21, 23 and 24 further include the detection of any endogenous multi-copy DNA element, wherein the multi-copy DNA element is not defined in terms of any particular type of sequence, the nucleotide sequence, length of the sequence, number of copies or location of the sequence within the genome. While claims 6 and 17 are limited to multi-copy DNA elements selected from any Alu, ERV, SINE, LINE and L1 sequence, these claims do not define the Alu, ERV, SINE, LINE and L1 sequences in terms of a particular nucleotide sequence, number of copies of the sequence, or its location within the genome.

Claims 7-10 and 24 encompass methods wherein the DNA containing the hypomethylated sequence and multi-copy DNA element are obtained from any prokaryotic or eukaryotic organism. Claims 1-6, 11-19 and 23 are inclusive of methods wherein the DNA containing the hypomethylated sequence and multi-copy DNA element are obtained from any prokaryotic or eukaryotic organism. As set forth on page 5 of the specification, the eukaryotic organism may be any plant, fungi or animal, including all mammals and humans.

Claims 1-8, 10-11, 13-21, 23 and 24 are inclusive of methods which detect any of all possible diseases or non-Mendelian diseases, any epigenetic abnormality associated with said diseases, chromosomal regions associated with said diseases, and coding regions that have altered expression patterns that contribute to said diseases. The claims thereby include the diagnosis of such widely diverse diseases such as Alzheimer's disease, cancer, Crohn's disease, hypertension, diabetes, fragile-X syndrome etc. These diseases differ significantly with respect to their etiology and symptoms. Further, the diseases differ significantly with respect to the genes and types of genes that are associated with their occurrence. Claims 9 and 16 are limited to methods which detect any type of bipolar disorder, including type I and type II, Clycothymia, bipolar disorder NOS, and forms of bipolar disorder exhibited by non-human organisms.

Claims 1-3, 5, 6, 10-19, 23 and 24 are inclusive of methods of detecting a hypomethylated sequence and an endogenous multi-copy DNA element, wherein the hypomethylated sequence and multi-copy DNA element may be at any distance from

one another on a chromosome. Claims 7, 8, and 9 require that the hypomethylated sequence and multi-copy DNA element are proximal to one another. However, the specification does not define the term "proximal." Thereby, this term does not impart any particular distance between the hypomethylated sequence and multi-copy DNA element. Thus, the claims as broadly written encompass detecting hypomethylated sequences and multi-copy DNA elements that are within distinct genes and/or are located at substantial distances from one another in the same or in different chromosomes.

Additionally, while claim 13 is limited to methods wherein the sample is obtained from brain, and claim 14 is limited to methods wherein the sample is obtained from the frontal cortex or prefrontal cortex, the remaining claims encompass methods in which any type of biological sample is analyzed for a hypomethylated sequence and multi-copy DNA element. Such samples may include such diverse samples as blood, serum/plasma, urine, tears, saliva, lung tissue, feces, ascites fluid etc.

Nature of the Invention:

The claims are drawn to methods for detecting a disease or an epigenetic abnormality associated with a disease by assaying for hypomethylation of a sequence and the presence of a multi-copy DNA sequence. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

Teachings in the Specification and State of the Art:

The specification (pages 39-41) teaches a method for identifying the presence of AluI sequences in DNA samples containing hypomethylated DNA. In this method, genomic DNA is digested with a methylation-sensitive restriction enzyme, the digested DNA is separated on a gel, and digested DNA of a desired size, such as 4 kb, is isolated as representative of hypomethylated DNA. The hypomethylated DNA is amplified using primers complementary to Alu sequences. Alu PCR products are then cloned and compared to sequences in a database of human genomic sequences in order to determine the genomic location of the cloned sequences.

The sequence of the cloned Alu amplification products were determined and are provided in the specification as SEQ ID NO: 29-263.

The specification (page 40) teaches the results of performing the above method using DNA samples obtained from 2 Caucasian females with bipolar disorder, one Caucasian male with mood disorder NOS, four Caucasian males with schizophrenia, and 2 Caucasian male control subjects.

Based on the above analysis, it was determined that about half of the cloned Alu sequences (N=57) mapped to Yq11.2. The specification teaches that the closest gene to this Alu sequence is a testis transcript Y4. However, no information is provided regarding the hypomethylation of the testis transcript Y4, the frequency of hypomethylation of the testis transcript Y4 in subjects having a disease versus control subjects, or the expression level of testis transcript Y4 in subjects having a disease and in control subjects. Since the same Alu sequences were identified in bipolar subjects, schizophrenia patients and control subjects, it is highly unpredictable as to the

relevance of this Alu sequence and the testis transcript Y4, and what role, if any, hypomethylation of these sequences play in the occurrence of disease.

Regarding the 2 subjects with bipolar disorders, the specification (Table 2), discloses 5 genes in subject sample #43 and 1 gene in subject sample number 34 that are located near or within Alu sequences identified by the above analysis. However, the specification does not provide any information regarding the frequency of hypomethylation of these sequences in subjects having BP and in control subjects, and does not teach the expression level of these genes in BP subjects and control subjects. Accordingly, while the specification identifies 6 genes from 2 individuals that are located near or in the same gene as Alu sequences identified in hypomethylated DNA, the specification has not established that hypomethylation of these gene sequences and the presence of the Alu sequences are associated with the occurrence of BP disorder. Further, the results obtained with subject sample #43 were distinct from the results obtained with subject sample #34. In the absence of information regarding the hypomethylation of the identified sequences in a representative number of BP patients (and patients having different types of BP), the results obtained with each individual patient can be used to diagnose BP in the general population.

The specification (Table 2) also lists 5 gene sequences that are close to or within the same locus of Alu clones obtained from the 4 schizophrenia patients analyzed; and 5 gene sequences that are close to or within the same locus of Alu clones obtained from the 2 control patients analyzed.

A second analysis was then performed to identified Alu sequences that map to regions of putative linkage to "major psychosis." Regions of chromosomal DNA that were previously identified by investigators as possibly being linked to BP or schizophrenia and which map to regions of the cloned Alu sequences are listed in Table 3. The specification (pages 44-48 and Example 4) discusses a number of genes that may map to these chromosomal regions and which may be linked to the occurrence of BP or schizophrenia. Yet, no data is provided establishing that these sequences are hypomethylated in patients having BP and are not hypomethylated in control / normal subjects and/or that hypomethylation of these sequences is associated with a change in the level of expression of these sequences.

In Example 2, results are provided regarding the analysis of Alu sequences in 3 patients with Huntington's disease (HD) and in 4 controls. The specification (page 49) states that an Alu sequence located 4kb from the (CAG)n/(CTG)n repeat region of the HD gene was found to be amplified in the hypomethylated fraction of the striatum DNA of the 3 HD patients and not in the four controls. The Example 3, the above analysis was repeated in 10 HD patients and 10 controls using DNA extracted from cerebellum and striatum samples. The Alu sequence was found to be amplified in all 10 cerebellum samples from HD patients, but not in any of the cerebellum samples from control patients; the Alu repeat was amplified in 8 of 10 of the striatum samples from HD patients and in one striatum sample from a control subject. However, the specification does not disclose the sequence of the amplified Alu sequence. The specification also

does not specifically teach that the Alu sequence located 4kb from the repeat region is itself hypomethylated in subjects having HD.

In Example 5 (pages 55-57), the specification outlines a method for determining changes in expression of approximately 30 genes that have been previously linked to bipolar disorder or schizophrenia. In this method, mRNA from brain tissues is extracted, reverse transcribed and amplified by quantitative PCR (see page 56). However, the specification does not provide the results of performing such an analysis.

Further, while the prior art, such as Florl (British Journal of Cancer. 1999. 80(9): 1312-1321) discloses the occurrence of hypomethylation of LINE repeat sequences in human subjects having urothelial carcinoma, the specification does not contemplate methods for detecting these particular LINE sequences as indicative of urothelial or renal carcinoma. Accordingly, the specification cannot be relied upon as providing support for these embodiments.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide sufficient guidance to enable the skilled artisan to practice the claimed method of identifying hypomethylated sequences and multi-copy DNA elements for the purposes of diagnosing a disease, identifying an epigenetic abnormality associated with a disease, detecting a chromosomal region associated with a disease, or identifying a DNA sequence having an epigenetically altered expression pattern that contributes to a disease.

The specification has not established that the simultaneous occurrence of the presence of a hypomethylated sequence and a multi-copy repeat sequence indicates that an individual has or is susceptible to having a disease.

As discussed above, the specification provides the preliminary results of a study in which Alu sequences are cloned from regions that contain hypomethylated DNA. The specification does not specifically teach that these particular Alu sequences are hypomethylated. The specification further teaches genes, identified in a database, which share sequence identity to the cloned Alu sequences. However, the specification does not provide an analysis of the genomic DNA proximal or distant to the Alu sequences in the subjects that carry the Alu sequences. No information is provided on the degree to which the proximal or distant sequences are hypomethylated in subjects having bipolar disorders or any other disease. Further, no information is provided regarding the level of expression of the proximal or distant sequences. Thereby, the specification does not provide any examples in which both an Alu sequence is detected and a hypomethylated sequence is detected in individuals having a disorder.

The specification teaches that both control subjects and subjects having BP, schizophrenia and mood disorder NOS have Alu sequences present in hypomethylated fractions of genomic DNA. Thereby, it is highly unpredictable as to how one would interpret the results of a finding of the presence of Alu sequences in hypomethylated DNA fractions since such an occurrence is not specifically associated with the occurrence of disease.

Further, the specification has not established that the findings obtained with only two subjects having bipolar disorder can be extrapolated to all subjects having bipolar disorder. It is unclear as to how one would apply the results obtained in the specification since they are preliminary in nature. The results provide only the initial findings which may lead investigators to further analyze the sequences flanking the Alu repeats in order to try to identify coding sequences that are near the repeats and which are hypomethylated and which show a change in the level of expression. Only after such an analysis has been performed in a statistically significant population, would one then try to ascertain whether the results are predictive of the occurrence of a particular type of bipolar disease.

Regarding Huntington's disease, the specification does not disclose the sequence of the amplified Alu sequence and thereby does not provide sufficient guidance to enable the skilled artisan to specifically detect this particular Alu sequence. The specification also does not teach that the Alu sequence located 4kb from the repeat region is itself hypomethylated in subjects having HD. While the data provided in the specification establishes that an undefined Alu sequence is amplified in HD subjects and not in controls, this finding does not establish the occurrence of a hypomethylated Alu sequence and a multi-copy (CAG)n/(CTG)n repeat region in subject's having HD and the absence of hypomethylation of the Alu sequence in control subjects. Thereby, it is unclear as to how this data can be relied upon to establish enablement of the claimed invention. Also, the above results were obtained using cerebellum and striatum samples.

The specification has not established a universal relationship between the occurrence of disease and the presence of a hypomethylated sequence and a multi-copy DNA element, proximal to one another or located at any distance in the genome. The specification does not disclose any specific sequences that are hypomethylated in a statistically significant number of individuals having a disease and which are not hypomethylated in normal control subjects and which are "proximal" or at any distance to a particular multi-copy DNA element.

Further, even if Applicants established that the particular sequences of Alu repeats are hypomethylated in subjects having bipolar disorder, this disclosure would not be considered to be sufficient to enable the broadly claimed method for diagnosing any disease in any human or non-human by assaying for the presence of the Alu sequence and any nearby or distant hypomethylated sequence associated with a disease.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The unpredictability in detecting hypomethylation of DNA sequences as diagnostic of a disease is well accepted in the art. It is highly unpredictable as to which genes, and which sequences within a gene, would be expected to be hypomethylated in particular diseases. As clearly stated on page 51 of the specification, **"Identification of the actual genes, which are epigenetically dysregulated and increase the risk of major psychosis is not a simple task."** While the specification goes on to state that the method disclosed therein can be used to search for such genes, the specification

does not specifically teach any particular genes that epigenetically dysregulated and in which hypomethylation can be detected as indicative of disease.

Further, the results obtained with one gene sequence or multi-copy DNA element cannot be extrapolated to other gene sequences or multi-copy DNA elements since the effects of hypomethylation on gene expression and the occurrence of disease cannot be predicted. Similarly, the hypomethylation results obtained with one type of disease cannot be extrapolated to other types of disease. This finding is supported by the teachings of the specification wherein different diseases sequences were found to be hypomethylated in different diseases. Accordingly, it is highly unpredictable as to what would be the structure of a sequence that is hypomethylated and specific for a disease or which would be hypomethylated in a manner that it's expression would be altered and would contribute to the occurrence of a disease.

It is further unpredictable as to whether the results obtained with two subjects having bipolar disease (or with one the limited number of subjects having mood disorder NOS and schizophrenia) can be extrapolated to the general population.

The unpredictability of extrapolating the results obtained in the present specification to the general population and the unpredictability of diagnosing complex diseases such as BP, is supported by the teachings in the post filing date art of Petronis (American Journal of Medical Genetics. 2003. 123C:65-75). Petronis (page 70) teaches that "As has typically been found in psychiatric genetics, both linkage and association studies of chromosome 11p markers and BD led to controversial findings, and despite significant effort, the role of chromosome 11p genes in etiopathogenesis of BD remains

unclear." Petronis (page 70) also states that "we detected that DRD2 methylation patterns exhibit numerous epG differences across individuals." The reference also teaches that methylation patterns and effects may vary with age and with sex.

It is also highly unpredictable as to whether the results obtained with Alu sequences in humans can be extrapolated to a representative number of other types of organisms, including prokaryotic organisms or other eukaryotic organisms, such as fungi, any plant, or any mammalian (dogs, horses, elephants etc). It is highly unpredictable as to whether hypomethylation occurs in prokaryotic organisms and can be detected as diagnostic of a disease or condition. Further, it is highly unpredictable as to what multi-copy DNA sequences exist in fungi, plants, vertebrates etc and which are proximal to a hypomethylated sequence and which could be detected as diagnostic of a disease.

As broadly written, the claims encompass methods in which any type of biological sample is analyzed for the presence of a hypomethylated sequence and multi-copy DNA element. The biological sample may include such diverse samples as blood, serum/plasma, urine, tears, saliva, lung tissue, feces, ascites fluid etc. However, it is unpredictable as to whether the results obtained with one type of sample can be extrapolated to all other types of biological samples. For instance, regarding HD, the results were obtained using genomic DNA samples obtained from the cerebellum and striatum. However, it is well known in the art that the expression of genes associated with the occurrence of disease is often tissue specific. Further, hypomethylation patterns may differ significantly between tissue types. The specification does not teach

a representative number of biological samples, in addition to cerebellum and striatum samples, that show hypomethylation and/or amplification of the Alu sequence located approximately 4kb from the (CAG)n/(CTG)n repeat region. With respect to the analysis of BP and schizophrenia patients, the specification (page 38) teaches that brain tissues were analyzed for the presence of Alu sequences. The specification does not state the particular region of the brain from which the sample was derived. It is highly unpredictable as to which particular regions of the brain exhibit a change in hypomethylation in BP and schizophrenia patients as compared to controls. It is also unpredictable as to which, if any, non-brain tissue could be analyzed for the occurrence of hypomethylation of specific genes as indicative of BP, or schizophrenia, or any other disorder. This unpredictability is supported by the teachings of Petronis (page 70), wherein it is stated that tissue specific differences in gene expression may be a result of differences in methylation patterns and effects. In particular, Petronis (page 70) states:

"DRD4, TH, or any other genes may exhibit epiG differential expression in different brain regions, and some alleles of such genes may be predisposing to one subtype of BD (e.g., early onset), while other alleles of the same genes may increase the risk to another subtype of BD (e.g., late onset). It is evident that if genetic studies are performed in an undifferentiated sample of BD, and depending on which subtype is predominant, evidence for association can be seen for different alleles."

Petronis (pages 72-73) also states that:

"Experimental epiG studies of complex diseases, however, are making the first steps (with the exception of cancer), and there are numerous logistic, methodological, and technical issues that will have to be addressed. First of all, for epiG studies, a tissue where the disease process originates is absolutely necessary. This means that in the case of BD, brain tissues should be investigated. Even if brain tissues are available, the next immediate complexity is to decide on what specific region of the very complex organ should be investigated, or even maybe selection of a brain region is not sufficient, and it is necessary to focus on some specific cells."

Working Examples:

The specification teaches methods for detecting the presence of Alu sequences present in hypomethylated DNA samples obtained from human subjects wherein said human subjects have bipolar disorder, schizophrenia, mood disorder NSO or Huntington's disease or are control/normal subjects. The specification also exemplifies the Alu sequences of SEQ ID NO: 29-263.

However, the specification does not exemplify any methods of diagnosing a disease or detecting an epigenetic abnormality associated with a disease by detecting the presence of a locus comprising a hypomethylated sequence that is specific for a disease and an endogenous multi-copy DNA sequence. In particular, the specification does not teach using such a methodology to diagnose bipolar I, bipolar II, bipolar NSO or Clycothymia.

The specification does not exemplify any methods in which a DNA coding sequences having an epigenetically altered expression pattern that contributes to a disease in an organism is detected by assaying for the presence of a locus comprising hypomethylated DNA and an endogenous multi-copy DNA element.

The specification does not exemplify any methods of detecting a hypomethylated sequence and a multi-copy element in a prokaryotic organism, in a fungi, plant or non-human organism, and the application of such a method for the diagnosis of a disease or an epigenetic abnormality associated with a disease.

All results provided in the specification pertain to the analysis of Alu sequences. The specification does not provide any working examples in which other types of multi-

copy DNA elements, such as microsatellite, ERV, SINE, LINE, or LI sequences are detected, together with a hypomethylated sequence, as diagnostic of a disease.

Lastly, the specification teaches the analysis of hypomethylated genomic DNA in samples obtained from brain, and particularly in cerebellum and striatum brain tissues. However, the specification does not exemplify methods in which a representative number of non-brain tissue samples, including blood, serum/plasma, ascites fluid, feces, urine, etc, are analyzed for the presence of hypomethylated sequence and a multi-copy DNA element as diagnostic of a disease or an epigenetic abnormality associated with a disease.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach any loci that comprise a hypomethylated sequence that is specific for a disease and which can be detected as indicative of the occurrence of a disease or as indicative of the presence of an epigenetic abnormality associate with a disease. Further, the specification does not teach any DNA coding sequences having an epigenetically altered expression pattern that contributes to a disease in an organism. Further, the specification does not teach a representative number of diseases associated with hypomethylation and the presence of a multi-copy DNA sequence in a representative number of organisms, including fungi, plants, any type of animal or prokaryotic organism. Accordingly, although the level of skill in the art of molecular biology is high, given the breadth of the claims, the lack of disclosure in the specification and in the prior art, and the unpredictability in the art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

Claim Rejections - 35 USC § 112 – Written Description

7. Claims 1-19, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claims 1-6 and 10-19 are drawn to methods for detecting an epigenetic abnormality associated with a disease comprising detecting a locus having a

hypomethylated sequence and an endogenous multi-copy DNA element. Claim 19 further includes the step of comparing expression patterns of a gene located proximal to said locus. Claim 7 is drawn to a method for identifying a chromosomal region associated with a disease state comprising detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element. Claims 8 and 9 are drawn to methods for identifying a DNA coding sequence having an epigenetically altered expression pattern comprising identifying a locus having a hypomethylated sequence and an endogenous multi-copy DNA element and comparing the expression patterns of DNA coding sequences. Claims 23 and 24 are drawn to methods for diagnosing a disease associated with an epigenetic abnormality comprising detecting a locus having a hypomethylated sequence and an endogenous multi-copy DNA element.

The claims as broadly written encompass the detection of any hypomethylated sequence wherein the sequence is not defined in terms of any particular chemical structure – e.g., a nucleotide sequence, it's location within a genome, the source of the sequence etc. Claims 1-5, 7-16, 18, 21, 23 and 24 further include the detection of any endogenous multi-copy DNA element, wherein the multi-copy DNA element is not defined in terms of any particular type of sequence, the nucleotide sequence, length of the sequence, number of copies or location of the sequence within the genome. While claims 6 and 17 are limited to multi-copy DNA elements selected from any Alu, ERV, SINE, LINE and L1 sequence, these claims do not define the Alu, ERV, SINE, LINE and L1 sequences in terms of a particular nucleotide sequence, number of copies of the sequence, or its location within the genome.

Additionally, claims 7-10 and 24 encompass methods wherein the DNA containing the hypomethylated sequence and multi-copy DNA element are obtained from any prokaryotic or eukaryotic organism. Claims 1-6, 11-19 and 23 are inclusive of methods wherein the DNA containing the hypomethylated sequence and multi-copy DNA element are obtained from any prokaryotic or eukaryotic organism. As set forth on page 5 of the specification, the eukaryotic organism may be any plant, fungi or animal, including all mammals and humans.

Accordingly, the claims encompass the detection of a significantly large genus of hypomethylated sequences and multi-copy DNA elements obtained from any prokaryotic or eukaryotic organism, wherein the presence of said hypomethylated sequence and multi-copy DNA element are diagnostic of any disease.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses Alu sequences consisting of the sequence of SEQ ID NO: 29-263. However, the specification does not disclose any particular gene sequences that contain these Alu sequences or which are "proximal" to the Alu sequences, and which are hypomethylated in subjects having a disease and/or whose expression is altered in individuals having a disease as compared to control subjects. Additionally, the disclosure of the particular Alu sequences obtained from human subjects having BP, schizophrenia or mood disorder NSO is not considered to be representative of the broadly claimed genus of any multi-copy DNA element (i.e., microsatellite, SINE, ERV, LINE, L1 sequence) obtained from any organism (prokaryotic, fungi, plant, non-human mammal etc), whose presence together with a hypomethylated sequence is diagnostic of any disease or any epigenetic abnormality associated with any disease.

Further, the specification (page 49) teaches that an Alu sequence located 4kb from the (CAG)n/(CTG)n repeat region of the HD gene was found to be preferentially amplified in the hypomethylated fraction of striatum and cerebellum DNA of HD patients as compared to controls. However, the specification does not provide the nucleotide

sequence for this Alu repeat. Further, the specification does not specifically teach that the Alu sequence itself is hypomethylated in HD patients, as compared to controls. The specification also does not teach a gene sequence containing the Alu repeat and the hypomethylation of such a gene sequence in HD patients as compared to controls.

Accordingly, the specification does not describe the complete chemical structure (e.g., nucleotide sequence) of a representative number of hypomethylated gene sequences and multi-copy DNA repeat sequences.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for the claimed hypomethylated sequences and multi-copy DNA elements.

However, the claims as written are inclusive of a potentially large genus of hypomethylated sequences and multi-copy DNA elements, obtained from any organism, and which are diagnostic for any disease. Given the limited amount of structural information regarding the claimed sequences, one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed methods, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification of nucleic acids. The particular nucleic acids themselves are required.

For these reasons, Applicants have not provided sufficient evidence that they

were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 10, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Florl et al (British Journal of Cancer. 1999. 80(9): 1312-1321).

Florl (page 1316 and 1318) teaches methods for detecting an epigenetic abnormality associated with a disease (urothelial carcinoma) wherein the method comprises detecting the presence of a hypomethylated LINE1 promoter sequence and a LINE1 endogenous multi-copy DNA element in the genome of a eukaryotic organism (i.e., humans). In particular, Florl (page 1318-1319) teaches that the LINE1 promoter sequence and the LINE repeat sequence are hypomethylated in bladder tissue samples from patients having urothelial carcinoma. As stated by Florl (page 1312, col. 2), LINE-1 is a repetitive retroelement

Regarding claims 2 and 3, Florl teaches separately detecting the presence of the hypomethylated LINE-1 promoter and the LINE-1 repeat sequence (see, e.g., Figures 4 and 5).

Regarding claim 4, the LINE-1 promoter is within 10kb of the LINE-1 multi-copy DNA element (see page 1318 col. 1 to 1319 col. 2, and page 1320, col. 1).

Regarding claims 5 and 6, Florl teaches that LINE-1 is a retroelement (page 1312, col. 2). Florl also teaches that this retroelement is strongly methylated in normal bladder (page 1316, col. 2).

Regarding claim 7, Florl teaches a method of identifying a locus that contains both a hypomethylated LINE1 promoter and a LINE-1 multi-copy DNA element, wherein the LINE1 promoter is methylated in normal/non-diseased bladder tissue (see pages 1316 and 1318 col. 2 to 1319, col. 1). It is a property of the chromosomal DNA that flanks this locus that it contains at least 1 coding sequence since chromosomal DNA has the property of containing coding sequences. It is noted that the specification and claims do not define the term "proximal" and thereby the coding sequence may be at any distance from the locus containing the LINE-1 promoter and repeat sequence. Further, it is noted that the present claims do not require performing an active process step of detecting a chromosomal region. As stated in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard*

Co., 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "identifying a chromosomal region associated with a disease" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight. Additionally, the LINE coding sequence is considered to be a chromosomal region comprising 1 coding sequence that is proximal (i.e., within) the locus.

Regarding claim 8, Florl teaches a method comprising identifying a locus that has a hypomethylated LINE-1 promoter sequence and an endogenous LINE-1 multi-copy DNA element, and comparing the expression pattern of LINE-1 of a disease sample to a non-disease sample (see pages 1316 and 1318 col. 1 to 1319). In the method of Florl, LINE-1 expression was detected in bladder carcinoma cell lines (i.e., a "diseased sample"), but was not detected in AV3 cell lines (see Figure 6). AV3 is considered to be a "non-diseased sample" since this sample was not derived from a bladder carcinoma cell line, but rather was derived from normal, human amnion (see page 1314).

Regarding claim 10, Florl (page 1316 and 1318-1319) teaches methods for detecting an epigenetic abnormality correlated with a disease wherein the method

comprises detecting the presence of a hypomethylated LINE1 promoter sequence and a LINE1 endogenous multi-copy DNA element in the genome of a eukaryotic organism (i.e., humans). The method of Florl is one in which the epigenetic abnormality correlated with a disease is hypomethylation correlated with urothelial carcinoma.

Regarding claims 23 and 24, as set forth above, Florl (pages 1316 and 1318, co. 2 to 1319, col. 1) teaches detecting a locus having a hypomethylated LINE-1 promoter and an endogenous LINE-1 multi-copy DNA element. Florl teaches an association between the LINE-1 promoter and endogenous LINE-1 element and the occurrence of urothelial carcinoma. Florl also teaches that the LINE-1 promoter is methylated in non-disease samples (page 1319). Further, it is noted that the present claims do not require performing an active process step of diagnosing a disease. As stated in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of a method "of detecting a disease..." is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly,

the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634